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Systolic time intervals and haemodynamic changes during intravenous infusion of prostaglandins $F_{2\alpha}$ and E_2

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SUMMARY The cardiovascular effects of prostaglandin $F_{2\alpha}$ and E_2 have been studied in 12 healthy pregnant women, in the first trimester. The investigation was carried out under general anaesthesia immediately after suction abortion. During intravenous infusion of the prostaglandin, the cardiac output, as well as the pressures in the pulmonary and femoral arteries were measured and the systolic time intervals were recorded.

Five women received prostaglandin $F_{2\alpha}$ in increasing doses from 100 μg/min to 300 μg/min. A significant rise was observed in cardiac output, pulmonary resistance, and femoral artery pressure. The peripheral resistance was unchanged while the pulmonary resistance was doubled, and a significant fall occurred in Po_2 together with a significant rise in Pco_2. Left ventricular ejection time (LVET) rose but not significantly whereas the pre-ejection period (PEP) and PEP/LVET fell significantly, and diastolic blood pressure/PEP (BPd/PEP) rose significantly.

Five women were given prostaglandin E_2 in doses increasing from 5 μg/min to 15 μg/min. During the infusion the cardiac output rose significantly, and there was a significant fall in femoral artery pressure and peripheral resistance. The pulmonary resistance and pulmonary artery pressure remained unchanged. LVET and BPd/PEP were unchanged, while both PEP and PEP/LVET showed a significant fall.

Two women received isotonic saline infusion and acted as control patients. Neither the haemodynamic measurements nor the systolic time intervals showed any significant changes during the period under study.

Prostaglandin $F_{2\alpha}$ has, on the one hand, a positive inotropic effect, but, on the other, increases the pulmonary artery pressure and changes the ventilation/perfusion ratio of the lungs in the wrong direction. Prostaglandin E_2 appears to cause only a moderate peripheral vasodilatation. Both compounds are used in gynaecology for abortion and the induction of labour. Because of cardiopulmonary effects prostaglandin E_2 should be preferred for clinical use. Patients with cardiopulmonary disease should not be given prostaglandin $F_{2\alpha}$.

The increasing use in recent years of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and E_2 (PGE_2) to produce abortion and to induce labour makes further knowledge of the cardiovascular effects of these drugs desirable. Animal experimental studies have produced divergent results, probably because of species differences and different methods as well as variations in dosage.[1–6] The results of studies in human beings on the haemodynamic action of $PGF_{2\alpha}$ have not been entirely consistent, but again the design of these studies has also varied considerably.[7–10] On the other hand, with PGE_2 the majority of investigators have found a fall in systemic arterial pressure and a rise in cardiac output.[11 12]

The effect of prostaglandin on left ventricular function has been studied only in animals. Both Nakona *et al.*[13] and Flerov and Ismailov[2] found increased ventricular contractility after the infusion of $PGF_{2\alpha}$ in anaesthetised dogs. The present study attempts to evaluate the effect of $PGF_{2\alpha}$ and PGE_2 in man on certain haemodynamic variables and left ventricular function by means of their measurement combined simultaneously with recordings of systolic time intervals.

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Subjects and methods

Patients were 12 pregnant women (age range: 17 to 41 years) admitted during the first trimester for legal abortion. All had given their written informed consent to participate in the investigation. The suction abortion was carried out in the routine manner, with the patient under general anaesthesia and, after its uncomplicated conclusion, the investigation was started immediately.

None of the women had a history of or clinical signs of heart disease (normal auscultatory findings, normal electrocardiogram and *x*-ray film of the chest).

The investigation was carried out in the following way.

(a) Introduction of a Swan-Ganz thermodilution catheter No. 7 via the right basilic vein, in such a manner that the thermister and hole in the tip were sited in the pulmonary artery and the side hole in the right atrium.

(b) Introduction of a short plastic catheter into the femoral artery.

(c) Recording of control values before the start of the infusion: pressure in the pulmonary and femoral arteries, measurement of the cardiac output and systolic time intervals, as well as blood gas analysis of arterial blood.

(d) *First infusion period* (0 to 10 minutes). Five patients were given an infusion of prostaglandin $F_{2\alpha}$, via a peripheral vein, five patients received prostaglandin E_2, and two patients isotonic saline. Prostaglandin $F_{2\alpha}$ was given at an infusion rate of 100 μg/min and E_2 at a rate of 5 μg/min. Seven minutes after the start of the period, blood was withdrawn for blood gas analysis; eight minutes after the start, the pressures in the pulmonary and femoral arteries were measured as well as the cardiac output and systolic time intervals.

(e) *Second infusion period* (10 to 20 minutes). The infusion rate for this period was 200 μg/min for $F_{2\alpha}$ and 10 μg/min for E_2. Blood sampling for gas analysis and the haemodynamic measurements were carried out as in period one.

(f) *Third infusion period* (20 to 30 minutes). The infusion rate during this period was 300 μg/min for $F_{2\alpha}$ and 15 μg/min for E_2. Blood gas analysis, haemodynamic measurements, and recording of the systolic time intervals were as in period one.

Determination of the *cardiac output* was carried out by injection of 5 ml of saline at 0°C into the right atrium and measurement of the fall in tempera-

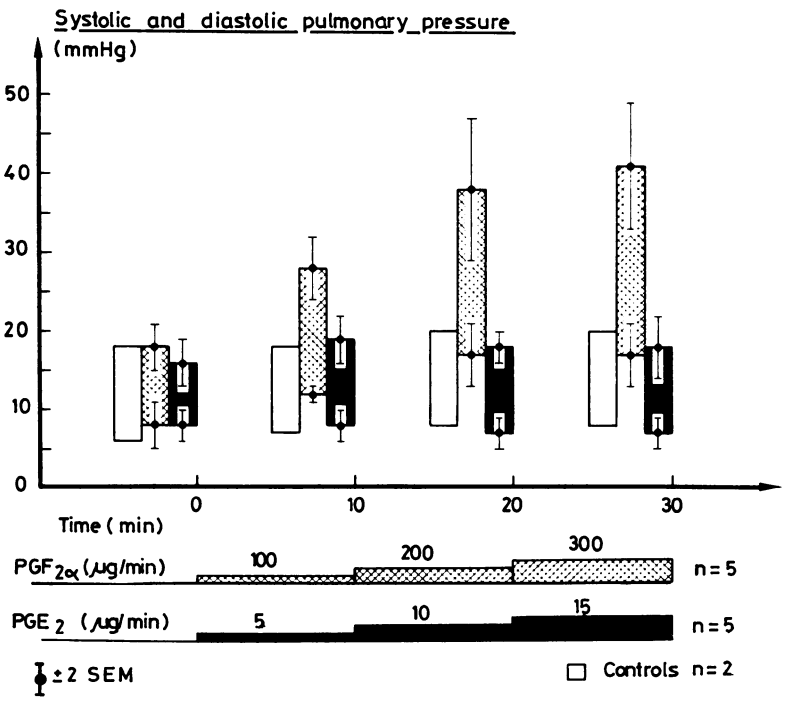

Fig. 1 *Systolic and diastolic pulmonary pressure in mmHg during intravenous infusion of prostaglandins $F_{2\alpha}$ and E_2 as well as in control patients (mean ± 2 SEM).*

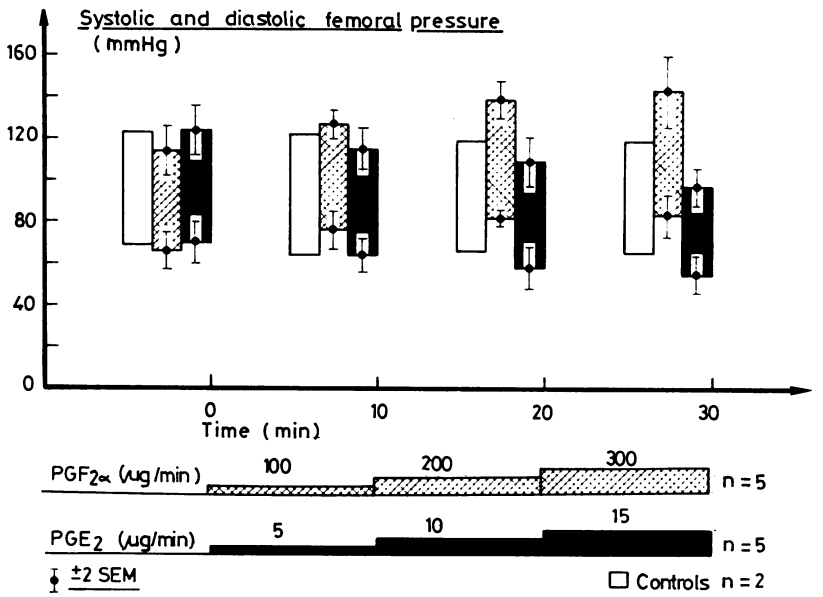

Fig. 2 *Systolic and diastolic systemic pressure in mmHg during intravenous infusion of prostaglandins $F_{2\alpha}$ and E_2 as well as in control patients (mean ±2 SEM).*

ture in the pulmonary artery. The cardiac output was calculated using a cardiac output computer (Edwards 9510) as the mean value of three consecutive measurements.

Pressure recording was carried out via the catheters inserted in the pulmonary and femoral arteries, with external transducers (Siemens-Elema 746). The zero point was the mid-axillary line. The pressures were recorded continuously during the whole investigation by a mingograph 82 (Siemens-Elma). Pulmonary resistance was calculated from cardiac output and the pressure difference between the diastolic and mean pulmonary pressures. The systemic vascular resistance was calculated from the cardiac output and the difference between the systemic blood pressure in the femoral artery and an estimated mean pressure in the right atrium of 3 mmHg.

Measurements of the systolic time intervals were performed from the simultaneous recording of an electrocardiogram (lead II), a phonocardiogram (filter max. 175 Hz), and a carotid pulse curve (membrane pelotte and Elema pressure transducer EMT 510 C). Measurement of the curves was carried out as described by Weissler *et al.*,[14] so that the total electromechanical systole (QS_2) was the time from the start of the QRS complex on the electrocardiogram to the start of the high frequency vibrations of the second heart sound on the phonocardiogram. Left ventricular ejection time (LVET) was measured on the carotid artery pulse curve from the start of the upstroke to the nadir of the incisural notch. The pre-ejection period (PEP) was equal to QS_2 minus LVET. All the measurements were carried out during apnoea and were later corrected for heart rate using the equations of Weissler *et al.*[14] The two ratios PEP/LVET and BP_d/PEP were calculated in addition to the individual systolic time intervals.

Blood gas samples were chilled and analysed immediately after each study (ABL-2, Radiometer).

Anaesthesia. All the patients were given the same type of intravenous anaesthesia, consisting of thiopentone sodium, pethidine, and pancuronium bromide. They were all intubated and ventilated on a Manley respirator using a nitrous oxide/oxygen mixture as the basic anaesthetic gas.

STATISTICAL METHODS

Friedmann's non-parametric variance analysis was used for the comparison of serial measurements of the individual variables. Linear regression analysis was used to evaluate the relation between systolic time intervals and individual haemodynamic variables.

Results

Fig. 1 shows the changes in the pulmonary circulation. After infusion of $F_{2\alpha}$ a significant rise could be seen in both the blood pressure and blood pressure amplitude. This rise took place during the first period. The percentage increase in the mean pressure in the $F_{2\alpha}$ group reached a maximum of 125. No definite changes could be seen in the pressure or pressure amplitude in the E_2 group.

Fig. 2 shows the changes in the systemic circulation. The infusion of $F_{2\alpha}$ produced a significant rise in pressure but caused no change in the pressure amplitude. The maximum increase in the mean pressure constituted 25 per cent of the initial value. After infusion of E_2, a significant fall was seen in the pressure but no change in the blood pressure amplitude. The maximum fall in mean pressure was 22 per cent of the initial value.

Fig. 3 shows that the cardiac output rose significantly after infusion of both $F_{2\alpha}$ and E_2. In addition the heart rate rose slightly during infusion of $PGF_{2\alpha}$, but the increase was only significant after E_2. The stroke volume rose significantly after the infusion of $PGF_{2\alpha}$ while only a slight increase occurred after the infusion of E_2.

Fig. 4 shows that there was a sharp rise of 100 per cent of the initial value in the calculated pulmonary resistance after the infusion of $PGF_{2\alpha}$, while this variable remained unchanged after E_2. The calculated systemic resistance fell after the infusion of both compounds, but only significantly after E_2.

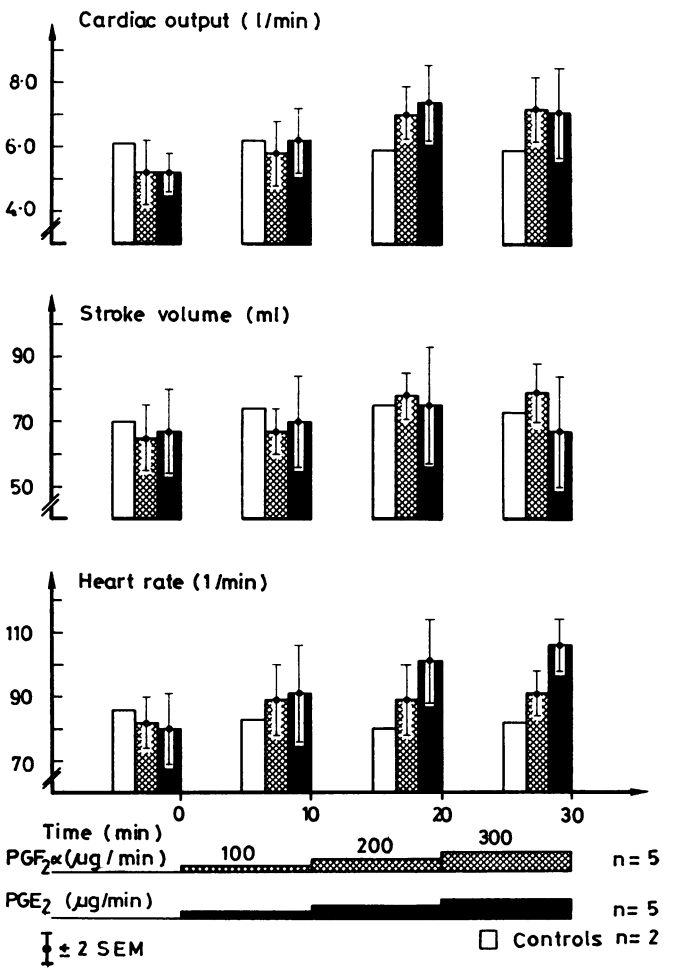

Fig. 3 *Mean values (±2 SEM) in cardiac output (l/min), stroke volume (ml), and heart rate per min during intravenous infusion of prostaglandins $F_{2\alpha}$ and F_2 as well as in control patients.*

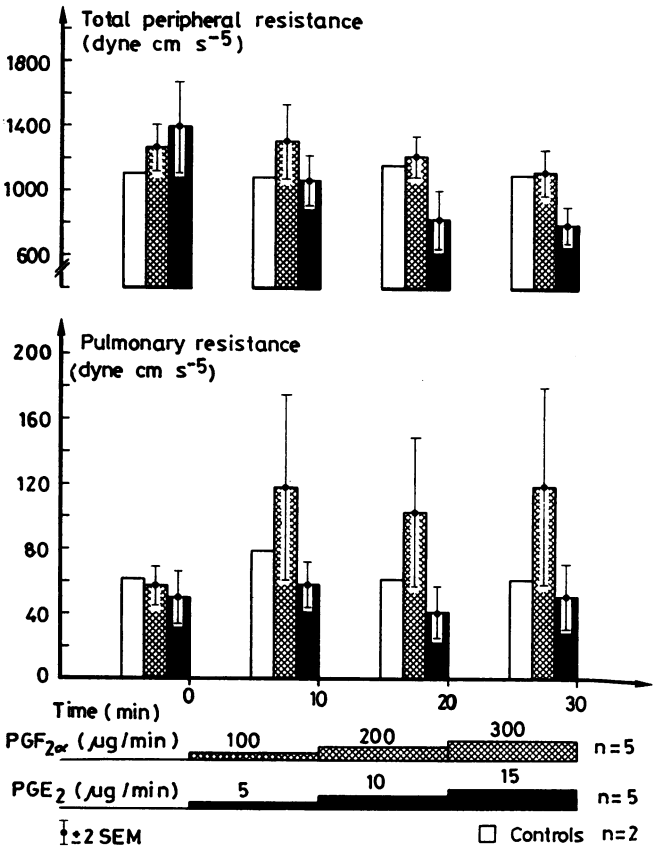

Fig. 4 *Mean values (±2 SEM) in total peripheral resistance and pulmonary vascular resistance (dyne cm s⁻⁵) during intravenous infusion of prostaglandins $F_{2\alpha}$ and E_2 as well as in control patients.*

Fig. 5 shows the changes in blood gases. A significant fall in Po_2 was observed in the $PGF_{2\alpha}$ group and a pronounced rise in the E_2 group. The Pco_2 increased significantly in the $F_{2\alpha}$ group while it remained unchanged in the E_2 group. The pH fell in both groups, though more in the $F_{2\alpha}$ group.

The QS_2 showed inconsistent changes. Fig. 6 and 7 show the changes in the remaining systolic time intervals. LVET showed a slight but non-significant rise in both groups. PEP showed a significant fall in both the $PGF_{2\alpha}$ and E_2 groups, so that the lowest value was found during the third period of measurement. The PEP/LVET ratio showed a significant decrease both in the $F_{2\alpha}$ and E_2 groups. The non-invasive contraction index BPd/PEP rose significantly in the $PGF_{2\alpha}$ group, while in the E_2 group this remained almost unchanged.

The individual time intervals and derived indices were correlated with the cardiac output and the peripheral resistance as well as the pressures in the pulmonary and femoral arteries. None of the time intervals nor the derived indices was found to have a correlation with the pressures in the pulmonary or femoral arteries. The QS_2 was not correlated with any of the haemodynamic variables.

The Table shows the other correlated coefficients.

In the two control patients, no significant changes were observed in any of the measured or calculated values. Two patients in the $PGF_{2\alpha}$ group developed ventricular ectopics towards the end of period three, one showing ventricular bigeminy. The ectopics disappeared spontaneously after the infusion was stopped. All the patients in the $F_{2\alpha}$ group developed diarrhoea immediately after the conclusion of the investigation, but this did not occur in any of the remaining patients.

Discussion

$PGF_{2\alpha}$ and PGE_2 appear to be equally effective in

gynaecology, for both abortion and for the induction of labour.[15] In the present investigation the compounds have therefore been evaluated with regard to their cardiological effects and to determine whether or not they are equally suitable for such use.

A general difference between the patients in the present investigation and those of other studies concerned with the evaluation of the haemodynamic effects of prostaglandins was that the former were studied while under barbiturate anaesthesia, which has a myocardial depressive effect.[16 17] All the haemodynamic measurements were, however, normal at the start of the investigation, while the systolic time intervals and derived indices were all abnormal.

The haemodynamic changes after $PGF_{2\alpha}$ infusion were a rise in cardiac output and stroke volume, an observation that has not been reported previously.[8–10] The rises in pulmonary arterial pressure and pulmonary resistance found are in agreement with the work of Secher and Andersen,[10] while the rising pressure in the femoral artery has not been shown by others.[6 9] A possible explanation of these differences may be the barbiturate anaesthesia, or, alternatively, that in these other studies small doses of the compounds were used and that cardiac output was measured using an indirect method.

The considerable rise in pulmonary resistance as compared with the unchanged total peripheral resistance can be related to the higher concentration

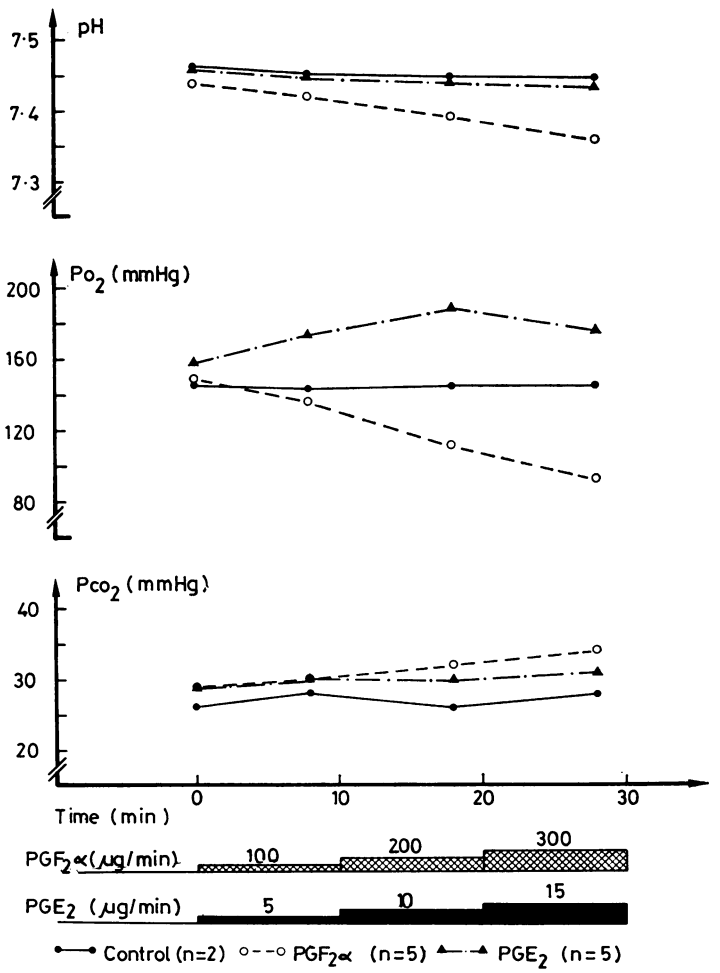

Fig. 5 *Mean values in pH, arterial Po_2 (mmHg), and Pco_2 (mmHg) during infusion of prostaglandins $F_{2\alpha}$ and E_2 as well as in control patients.*

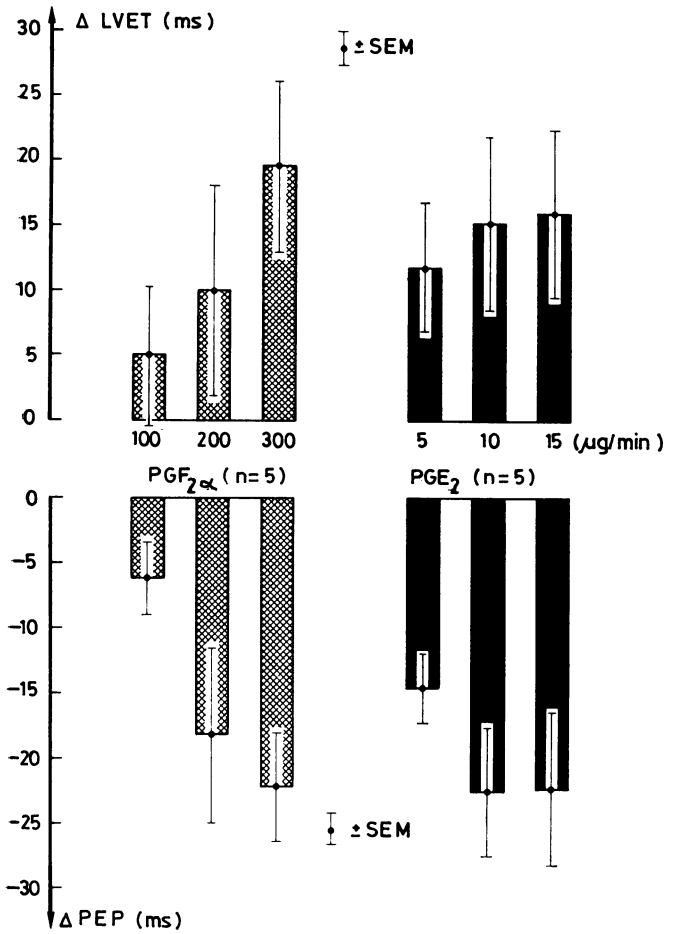

Fig. 6 *Changes from control values in left ventricular ejection time (LVET) and pre-ejection period (PEP) in ms after intravenous infusion of prostaglandins* $F_{2\alpha}$ *and* E_2 *(mean changes ±SEM).*

of $PGF_{2\alpha}$ in the pulmonary circulation because of a high clearance rate of this compound in the lungs.[18 19] The changes in acid-base status are in agreement with animal experimental investigations.[4 20] An explanation for the fall in Po_2 and the rise in Pco_2 must be found partly in the bronchoconstrictive properties of $PGF_{2\alpha}$,[21] and partly in the increased pulmonary resistance which results in a poorer ventilation/perfusion state, which has been found in patients after the infusion of 15-methyl $F_{2\alpha}$.[22]

Systolic time intervals reflect left ventricular function. A rise in the arterial blood pressure alone will cause a rise in the heart-rate-corrected intervals PEP, LVET, and QS_2.[23] Similarly, an isolated rise in cardiac output will produce a rise in the rate-corrected and LVET and a fall in PEP and PEP/LVET.[24] We would not have expected LVET to show the slight but non-significant rise that it did, when both the systemic pressure and the cardiac output rose, and this suggests that $PGF_{2\alpha}$ may counteract this rise. Neither did we expect that PEP would fall significantly; the rising blood pressure and cardiac output should affect PEP in opposite directions and produce no clear change. Thus, $PGF_{2\alpha}$ has a property which causes PEP to fall. Similarly, PEP/LVET falls and BP_d/PEP rises significantly. These changes in the systolic time intervals together with the significant increase in stroke volume strongly indicate a positive inotropic effect of $PGF_{2\alpha}$. A possible increase in preload would not produce these changes, since this will have the same effect on LVET as that of both the

rising cardiac output and rising systemic pressure. In this situation, PEP and PEP/LVET would only be slightly affected, and BP_d/PEP would not rise significantly.[25]

The effect of $PGF_{2\alpha}$ on the myometrium, where it improves contractility by increasing the concentration of Ca^{++} intracellularly, makes it probable that this compound produces a positive inotropic effect in a similar manner.

The haemodynamic changes found after infusion of prostaglandin E_2 are in accord with those in the published material.[3 10 12] There is a fall in the blood pressure in the femoral artery, a fall in the peripheral resistance, and a rise in cardiac output and heart rate. There are no definite changes in the acid-base status, but there is a tendency to a rise in Po_2. The changes in the systolic time intervals, with a slight rise in LVET, a significant fall in PEP and PEP/LVET, and an unchanged BP_d/PEP can all be explained simply from the haemodynamic changes observed.

The systolic time intervals did not correlate in any case with the right-sided haemodynamic variables. In the patients who received an infusion of prostaglandin E_2, a familiar relation was found between the various systolic time intervals and the haemodynamic variables. In contrast to this the cardiac output, stroke volume, and afterload were only poorly correlated or not at all to the changes in the systolic time intervals after infusion of $PGF_{2\alpha}$. This absence of inter-relation must be ascribed to the positive inotropic property of the compound.

The interpretation of systolic time intervals is often difficult, particularly in pharmacological studies, where the compounds can produce several haemodynamic changes. A conclusion regarding the cardiovascular effect of a compound based on systolic time intervals alone can therefore be flawed. In an investigation such as this one, where the haemodynamic effects of a compound are measured at the same time as the systolic time

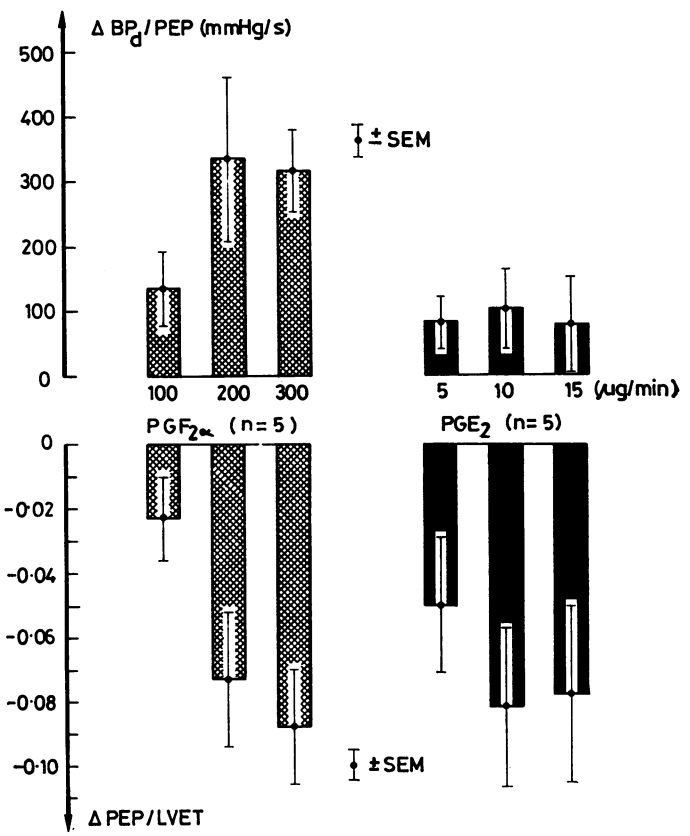

Fig. 7 *Changes from control values in the ratios systemic diastolic pressure to pre-ejection period (BP_d/PEP) in mmHg/s and pre-ejection period to left ventricular ejection time (PEP/LVET) during intravenous infusion of prostaglandins $F_{2\alpha}$ and E_2.*

Table *Linear regression coefficients between cardiac output and total peripheral resistance and each systolic time interval and derived indices during intravenous infusion of prostaglandins $F_{2\alpha}$ and E_2*

	$F_{2\alpha}$		E_2	
	Cardiac output	*Total peripheral resistance*	*Cardiac output*	*Total peripheral resistance*
LVET	0·29	0·22	0·66**	−0·77***
PEP	0·46*	0·47*	−0·73***	0·69***
PEP/LVET	0·43	0·43	−0·71***	0·70***
BPd/PEP	0·68***	—	0·47*	—

LVET, left ventricular ejection time; PEP, pre-ejection period; BPd, systemic diastolic pressure.
* $p < 0·05$, ** $p < 0·01$, *** $p < 0·001$.

intervals, the latter can help in the search for the causes of the former.

With this in mind, the changes in PEP, PEP/LVET, and BP_d/PEP all appear to reflect the positive inotropic effect of prostaglandin $F_{2\alpha}$ on the heart, and the cardiac response to the reduction in peripheral systemic resistance after prostaglandin E_2, respectively.

Thus, prostaglandin $F_{2\alpha}$ appears to be less suited for the induction of abortion and the induction of labour because of the effects on the lungs and the pulmonary circulation. It should not be given to patients with cardiopulmonary disease. The limited haemodynamic action of prostaglandin E_2 makes this more suitable for clinical use, as it produces only peripheral vasodilatation, which can be monitored simply by measuring the blood pressure. The compound seems well suited for use in patients with lung disease because of the slight rise in Po_2 which it appears to produce.

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